CLINICOPATHOLOGICAL STUDY AND PROGNOSTIC FACTORS IN RADICAL CYSTECTOMY

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CERTIFICATE

I hereby certify that this is the bonafide work done by **B. JAYANAND SUNIL** who is appearing for **MCh Surgical Oncology Branch VII** examination in February 2008, under my guidance in the College of Oncological Sciences, Cancer Institute (WIA), Adyar, Chennai.

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CONTENTS

OBJECTIVE

1. To study the recurrence pattern and disease-free survival of patients undergoing radical cystectomy for bladder cancer
2. To study the effect of lymphadenectomy on recurrence in bladder cancer after radical cystectomy
3. To study the prognostic factors governing disease-free survival after radical cystectomy
4. To do a descriptive analysis of patients undergoing radical cystectomy, to study the morbidity pattern and the quality of life after surgery

MATERIALS AND METHODOLOGY

From January 2001 to March 2007, 37 patients underwent radical cystectomy for bladder cancer. These patients were followed up till October 2007. The recurrence pattern and the time to recurrence were studied at follow up. Prognostic factors such as histology, age, grade and stage of the disease that influence the survival and recurrence were studied. The extent of lymphadenectomy and pathological nodal status were correlated with the recurrence. The analysis was done using the SPSS 11.0.1 (15 Nov 2001) statistical package.

REVIEW OF LITERATURE

EPIDEMIOLOGY

Fifty-four thousand new cases of bladder cancer are diagnosed each year. It is the second most common genitourinary cancer and results in over 12,000 cancer-related deaths annually. Twenty percent to 25% of newly diagnosed bladder cancer consist of muscle-invasive disease, with majority of these invasive bladder cancers demonstrating invasion at the time of diagnosis. While tumor grade and stage do influence progression, only approximately 15% of superficial tumors will eventually develop the characteristic features of muscle-invasion. For those that become muscle-invasive, however, the risk of metastasis and mortality unquestionably and dramatically rises.

More than 90% of invasive and noninvasive bladder tumors are transitional cell carcinomas (TCCs). Invasive bladder cancer can however be of squamous cell carcinoma(3%), adenocarcinoma(2%), or small cell carcinoma(<1%) origin. TCCs may also contain focal areas of

squamous or glandular differentiation. These have been traditionally classified and managed as TCC, but future investigation may demonstrate that these historical variants are in fact associated with different outcomes and should be treated as different pathologic entities.

Bladder cancer is 2.5 times more common in men than in women. Bladder cancer has rarely been found incidentally at autopsy. Bladder cancer incidence increases with age in both sexes. Males have a higher 5-year survival rates than women. Survival by stage at presentation is more favorable for whites. Although the vast majority of bladder cancers in both sexes and races are TCCs, a higher proportion of bladder cancers other than TCCs occur in African Americans and in females, and the relative poor outcomes from these tumors may explain some of the racial and sex differences in bladder cancer mortality as well.

The crude incidence rate of bladder cancer in males according to the Madras Metropolitan Tumor Registry is 2.1/100,000 population, and in females it is 0.8/100,000. In India, the crude incidence rate of bladder cancer in males and females is 2.4 and 0.7/100,000 population respectively. In the world, the crude incidence rate of bladder cancer in males and females is 25.4 and 8.54/100,000 population respectively.

Since the 1950s, the incidence of bladder cancer has risen by approximately 50%. In comparison, there has been a decrease in bladder cancer's mortality rate during the same interval by approximately 33%. The reduction in mortality has been primarily achieved in men. The median age at diagnosis for TCC in men is 69 years and in females is 71 yrs. Younger patients appear to have a more favorable prognosis because they present more frequently with superficial, low-grade tumors; however, the risk for disease progression is the same, grade-for-grade, in younger patients as in older ones.

ETIOLOGY

Factors reported to be causally related to bladder cancer's development and progression include occupational exposure to chemicals; cigarette smoking; coffee drinking; ingestion of analgesics or artificial sweeteners; bacterial, parasitic, fungal, and viral infections; harboring of bladder calculi, and receiving genotoxic chemotherapeutic agents. Carcinogen produce lesions in the DNA of target cells, both initiating and propagating the process of tumorigenesis. It is likely that multiple lesions are required to cause malignant transformation of cells.

Oncogenes that have been associated with bladder cancer include those of the ras gene family, including the p21 ras oncogene, which in some studies, has been found to correlate with higher histologic grade. This is a GTPase, transducing signals from the cell membrane to the nucleus, affecting proliferation and differentiation.

Several tumor suppressor gene loci have been closely associated with bladder cancer. These include that of the p53 gene on chromosome 17p; retinoblastoma (Rb) gene on chromosome 13q; genes on chromosome 9p in the region 9p21 where the genes for the p19 and p16 chromosomes reside. Impaired p53 function contributes to an aggressive phenotype and paradoxically enhances sensitivity to some chemotherapeutic agents. Reduced or abnormal expression/function of the products of the genes coding for p15, p16, p21, p27, or pRb would be expected to result in uninhibited proliferation and perhaps malignant transformation and tumor progression.

Abnormal expression of the receptor for Epidermal growth factor (EGF) occurs in bladder cells and that increased expression is associated with more aggressive biologic behaviour. EGF receptor signaling induces not only growth, but also cancer cell motility.

Chemicals that have been shown to be carcinogens for bladder cancer include aniline dyes, 2-naphtylamine, 4-aminobiphenyl, benzidine, 4-nitrobiphenyl and 2-amino-1-naphthol. Most bladder carcinogens are aromatic amines. Occupational exposure accounts for 20% of bladder cancer cases, with long latency periods (30-50 years). This is probably related to cumulative dose.

Cigarette smokers have up to four-fold higher incidence of bladder cancer than do people who have never smoked. The risk correlates with the number of cigarettes smoked, the duration of smoking, and the degree of inhalation of smoke. The risk is observed in both the sexes. The reduction of this risk down to baseline takes nearly 20 years after cessation. The failure to quit smoking once a diagnosis is made predicts a more ominous outcome.

Consumption of large quantities of analgesic combinations containing phenacetin is associated with increased risk of transitional cell carcinoma of the renal pelvis and bladder.

Chronic cystitis in the presence of indwelling catheters or calculi is associated with increased risk of squamous cell carcinoma of the bladder. Two to 10% of paraplegics with long-term indwelling catheters

develop bladder cancer, 80% of which are squamous carcinomas. There is also an increased incidence of transitional cell carcinomas in males with *Schistosoma haematobium* cystitis.

Ectopia vesicae is associated with increased risk of bladder cancer. They develop adenocarcinoma of the bladder.

Patients treated with radiotherapy for carcinoma of uterine cervix or rectum have a 2-4 fold increase in risk of developing bladder cancer subsequently. The incidence increases if chemotherapy was also administered (with or without cyclophosphamide) or even if chemotherapy was used alone. The risks of all groups continue to rise after 10 years. These tumors are usually of high grade and locally advanced at the time of diagnosis.

DIAGNOSIS

All patients suspected of having bladder cancer should have careful cystoscopy. Cystoscopic examination is required to confirm the presence of malignancy, characterize its architecture, determine the multiplicity of disease, and determine whether there is diffuse mucosal involvement. Abnormal areas should be biopsied. Random biopsy of

endoscopically normal areas of urothelium are no longer taken routinely as part of the standard diagnostic approach in the evaluation of a bladder cancer diasthesis when a preliminary cytology has been negative.

Malignant urothelial cells can be observed on microscopic examination of the urinary sediment or bladder washings. Characteristically, tumor cells have large nuclei with irregular, coarsely textured chromatin. Microscopic cytology is more sensitive in patients with high-grade tumors or carcinoma-in-situ. False positive cytology may occur in 1-12% cases due to urothelial atypia, inflammation, or changes caused by radiation or chemotherapy. It has been estimated that the sensitivity of a single barbotage specimen is equivalent to tthat of three voided specimens.

PATHOLOGY

Normal Bladder Urothelium

The urothelium of the normal bladder is 3-7 layers thick. There is a basal cell layer on which rests one or more layers of intermediate cells. The most superficial layer is composed of large, flat, umbrella cells. The urothelium rests on the lamina propria basement membrane.

CARCINOMA IN SITU

Carcinoma in situ may appear as a velvety patch of erythematous mucosa, although quite often it is endoscopically invisible. Histologically, it consists of poorly differentiated transitional cell carcinoma confined to the urothelium. Urine cytology is positive in 80-90% of patients with carcinoma in situ. About 20% of patients treated with cystectomy for diffuse carcinoma in situ are found to have microscopic muscle invasive carcinoma.

TRANSITIONAL CELL CARCINOMA

More than 90% of bladder cancers are transitional cell carcinomas. WHO and the ISUP prefer the term Urothelial cancers. They manifest in a variety of patterns of tumor growth including papillary, sessile, infiltrating, nodular, mixed, and flat intraepithelial growth. Histologically, there are increased number of epithelial cell layers with papillary foldings of the mucosa, loss of cell polarity, abnormal cell maturation from basal to superficial layers, increased nuclear-cytoplasmic ratio and increased number of mitosis. Approximately, 70% of bladder tumors are papillary, 10% are nodular, and 20% are mixed.

GRADING

Grading systems are based on the degree of anaplasia of the tumor cells. At a consensus conference, the WHO and the ISUP decided to classify many of these tumors as papillary urothelial neoplasms.

A papilloma (grade 0) is a papillary lesion with a fine fibrovascular core covered by normal bladder mucosa. It does not have more than seven epithelial layers nor any abnormalities in histology. It is a rare, benign neoplasm and never recurs after endoscopic resection.

Well differentiated (grade I) tumors have thin fibrovascular stalk with thickened urothelium containing more than seven cell layers, with cells exhibiting only slight anaplasia and pleomorphism. There are only rare mitotic figures. When they are mucosally confined, these have been termed papillary urothelial tumors of low malignant potential (LMP). They often recur, and recurrences may be of higher grade and stage. They share the same molecular and prognostic feature as grade II cancers.

Moderately differentiated (grade II) tumors have a wider fibrovascular core, a greater disturbance of the base-to-surface cellular maturation, and a loss of cell polarity. The nuclear-cytoplasmic ratio is higher. Mitotic figures are more frequent. These have been termed low-grade urothelial carcinomas in the new WHO and ISUP classification.

Poorly differentiated (grade III) tumors, named high-grade urothelial carcinoma in the new WHO and ISUP classification, have cells that do not differentiate as they progress from the basement membrane to the surface. Marked nuclear pleomorphism and high nuclear-cytoplasmic ratio is noted. Mitotic figures are frequent.

The presence of metaplastic elements like squamous carcinoma and adenocarcinoma in urothelial carcinoma does not change the principal classification of the tumor as a urothelial carcinoma.

SQUAMOUS CELL CARCINOMA (SCC)

These cancers occur, on the average, 10-20 years younger than patients with TCC. Bilharzial cancers are exophytic, nodular, fungating lesions that are usually well differentiated and have a relatively low incidence of lymph node and distant metastasis. This is due to capillary

and lymphatic fibrosis resulting from chronic infection. They are of relatively low histologic grade. Nonbilharzial SCC are usually caused by chronic irritation from urinary calculi, long-term indwelling catheter, chronic urinary infection, or bladder diverticula. Cigarette smoking is significantly associated with an increased risk of SCC. Male predominance is less striking in SCC. Its prognosis is poor as most patients have an advanced disease at presentation. Histologically, it consists characteristically of keratinized islands that contain eccentric aggregates of cells called squamous pearls. Cytology is of limited value in diagnosis. In bilharzial SCC, bone is the most common site of distant metastasis.

ADENOCARCINOMA

Adenocarcinomas account for less than 2% of primary bladder cancers. They are grouped as 1. primary vesical 2. urachal 3.metastatic. They also occur in intestinal urinary conduits, augmentations, pouches, and ureterosigmoidostomies. Primary vesical adenocarcinomas can occur in exstrophic bladders. Signet-ring cell carcinomas characteristically produce linitis plastica of the bladder. They are generally of poor prognosis as they are advanced stage at presentation. Urachal carcinomas are usually adenocarcinomas , have a sharp demarcation between the

tumor and the adjacent bladder epithelium, with the tumor being located in the bladder wall beneath the normal epithelium. When they invade the bladder lumen, they may produce mucus in urine. Histologically they exhibit wider and deeper infiltration of the bladder wall than expected. Metastatic adenocarcinomas are from primary in rectum, stomach, endometrium, breast, prostate, and ovary.

STAGING

The workup of a suspected bladder cancer should include a cytology, a cystoscopy and an upper tract study. The preference for the upper tract study is computed tomography (CT), as the ureter and the renal pelvis can be particularly visualized by the use of that technique as well as the relevant lymph nodes and the kidney parenchyma. Careful staging is important as treatment is dependent on the initial stage of the disease. The clinical stage of the primary tumor is determined by transurethral resection of the bladder tumor (TURBT). This resection should include a sample of the muscularis propria for appropriate diagnosis, particularly if the tumor appears sessile or high grade. Once the specimen has been removed, the base of the resected area should be

separately biopsied. Any suspicious areas in the remainder of the bladder should be biopsied, and a biopsy of the prostatic urethra is also done.

Patients who have documented muscularis propria –invasive bladder cancer require an additional set of investigations. CT scanning is the most commonly employed imaging modality for the staging of invasive bladder cancer for the evaluation of the pelvis and retroperitoneal lymph nodes. The correlation of CT findings with pathology of the cystectomy specimen is 65-80%. CT detects metastatic disease in regional lymph nodes in 50-85% cases.

Magnetic resonance imaging (MRI) has gained considerable popularity as an imaging technique for invasive bladder tumors. Failure to detect microscopic nodal disease with MRI is similar to that of CT. Understaging and overstaging remain persistent problems with both CT and MRI, occurring in about 30% of cases.

Preoperative bone scan is not necessary for patients with clinically organ confined, muscle invasive bladder cancer. For patients who have signs or symptoms suggestive of bone involvement, bone scan may provide additional information that could provide additional information that could change the therapeutic recommendations under consideration.

Suspicious bone scan results are correlated with MRI findings to increase diagnostic accuracy.

FDG-PET appears to be a useful modality in conjugation with conventional imaging studies for identifying distant sites of metastases. The detection of the primary tumor, local tumor recurrence, and regional pelvic lymph node metastases is limited due to the presence of excreted FDG in the urinary tract, the deficiency that is only partially overcome by continuous irrigation during the study. With the advent of new tracers that are not really excreted, PET may play a greater role in the diagnosis and locoregional staging of bladder cancer.

ANATOMY AND LYMPHATIC DRAINAGE

The urinary bladder is a muscular reservoir of urine, which lies in the anterior part of the pelvic cavity. An empty bladder is tetrahedral in shape and has an apex, directed forwards; a base or fundus, directed backwards; a neck, which is the lowest and most fixed part of the bladder; three surfaces, superior, and right and left inferolateral. The apex is connected to the umbilicus by the median umbilical ligament which represents the obliterated embryonic urachus. In the female, the base is related to the uterine cervix and to the vagina. In the male, the

upper part of the base is separated from the rectum by the rectovesical pouch and the coils of intestine; and the lower part is separated from the rectum by the seminal vesicles and the vasa deferentia. The triangular area between the two deferent ducts is separated from the rectum by the rectovesical fascia of Denonvilliers. The neck is the lowest and most fixed part of the bladder. In males, it rests on the base of the prostate with which its walls are continuous. In females, it is related to the pelvic fascia which surrounds the upper part of the urethra. The inferolateral surfaces of the bladder are devoid of peritoneum, and are separated from each other anteriorly by the anterior border, and from the superior surface by the lateral borders. In the males, each surface is related to the pubis, the puboprostatic ligaments, the retropubic fat, the levator ani and the obturator internus. In the females, the relations are the same, except that the puboprostatic ligaments are replaced by the pubovesical ligaments. In an empty bladder, the greater part of the mucosa shows irregular folds due to its loose attachment to the muscular coat. In a small area over the lower part of the base of the bladder, the mucosa is smooth due to its firm attachment to the muscular coat. This area is the trigone of the bladder. The internal urethral orifice is located at the apex of the trigone. The ureters open at the posterolateral angles of the

trigone. The main arterial supply of the bladder comes from the superior and inferior vesical arteries, branches of the anterior trunk of the internal iliac artery. Additional supply is derived from the obturator, inferior gluteal arteries; and in females, from the uterine and vaginal arteries. Venous drainage is into the vesical venous plexus on the inferolateral surfaces of the bladder. Veins from this plexus pass backwards in the posterior ligaments of the bladder, and drain into the internal iliac veins. Most of the lymphatics from the urinary bladder terminate in the external iliac nodes. Some anterior and lateral drainage may go through the obturator and internal iliac nodes, whereas portions of the bladder base and trigone may drain into the internal and common iliac groups. The common iliac nodes receive efferent vessels from the external and internal iliac nodes and the pelvic ureter and drain into the lateral aortic nodes.

MANAGEMENT OF SUPERFICIAL AND MUSCLE INVASIVE BLADDER CANCERS

The term superficial bladder cancer refers to Ta, T1 and Tis lesions of any grade. The principal technique for the diagnosis and management of superficial bladder lesions remains endoscopic management, generally by cystoscopy and TURBT. After complete

resection, normal muscle fibers should be visible at the base. When a repeat TUR is performed within several days to weeks of the original procedure, residual tissue may be seen in as high as 40-75% of cases. In the evaluation of T1 tumors specifically, a repeat TUR can demonstrate worse prognostic findings in up to 25% of specimens. The Nd:YAG laser has been employed for patients with superficial bladder cancers with recurrent low grade lesions. Little bleeding occurs. High cost, absence of available tissue for pathological analysis and risk of perforation due to forward scatter of laser energy are the disadvantages. Photodynamic therapy has been studied in Tis and papillary T1 lesions with a response rate of 50-60%.

Intravesical therapy can serve as adjuvant treatment, as therapy for residual disease, or as a means of disease prophylaxis. The goal of intravesical therapy with chemotherapeutic agents is to decrease recurrence, prevent progression, and eradicate residual disease after TURBT. The ideal agent would be inexpensive; have minimal toxicity, either locally or systemically; and be administered in a single dose. BCG remains the most effective form of intravesical therapy for prophylaxis and treatment of superficial bladder cancer. BCG accumulates and adheres to the bladder wall. It is then internalsed and processed by

professional APC and tumor cells. BCG antigens are presented via MHC class II molecules to CD-4 T cells and via MHC class I molecules to CD-8 T cells. Production of chemokines such as IL-8 contributes to the local activation of the immune system. Activated leucocytes and mononuclear cells invade the bladder wall. Th1 response occurs with particular cytokines (IFN-y,IL-2,IL-12 and TNF-b). This cytokine profile promotes delayed type hypersensitivity response, cytotoxic cell response, macrophage activation or cellular immune inflammatory reaction. The Th1 cytokine profile enables recruitment and maturation of cytotoxic effector cells. Some of the cytokines, NK cells and BCG itself, may exhibit a direct cytotoxic effect on tumor cells. Mitomycin C, Doxorubicin, Epirubicin, Thiotepa and Valrubicin are chemotherapeutic agents that can be used for intravesical chemotherapy.

Indications for Intravesical therapy:

1. Multifocal Tis
2. Tis with residual Tis or Ta lesion
3. Rapid recurrence after TURBT
4. Prophylaxis after complete TURBT for T1 lesions and high grade Ta lesions

The role of radiation therapy in the treatment of superficial bladder cancer is limited and generally restricted to those individuals who refuse cystectomy after the failure of intravesical therapy or who are unsuitable for major surgery.

The use of cystectomy in the treatment of superficial bladder cancer must be evaluated in terms of the benefits and limitations of current intravesical therapy, the morbidity of major surgery, and our ability to predict the potential progression of high-risk superficial disease in individuals. Radical cystoprostatectomy in the male patient and anterior pelvic exenteration in the female patient, coupled with en bloc pelvic lymphadenectomy , remains the standard surgical approaches to muscle invasive bladder carcinoma in the absence of metastatic disease. Despite alternatives that may appear appealing and may be appropriate for certain individuals, surgical removal still provides local control and chance for cure, to which other treatments attempt to compare themselves.

Indications for Radical cystectomy:

1. Persistent/recurrent high-risk superficial disease who failed intravesical therapy
2. Muscle invasive TCC in the absence of metastasis

3. Multifocal T1 grade III
4. T1 grade III with Tis
5. Rapid recurrence after intravesical therapy especially if multifocal
6. Involvement of prostatic stroma
7. Concomittent Tis of urethra
8. Failure of bladder preservation-chemoradiation
9. Tumor arising in bladder diverticula

The patient's health status is optimized prior to cystectomy. Age and co morbidities should not be used as absolute deterrents when considering radical cystectomy as therapy for a potentially lethal cancer. Patients are seen preoperatively by an enterostomal nurse for counseling and optimal stoma site marking. This is recommended regardless of diversion type planned in the event that an orthotopic diversion is not technically feasible or contraindicated. Prior to surgery, patients undergo a mechanical and antibiotic bowel preparation usually performed in the out patient setting after 1-2 days of clear liquid diet. Patients are routinely admitted one day prior to surgery with an estimated length of stay between 10 and 14 days.

In a male, the prostate and seminal vesicles are removed routinely along with the bladder and is equivalent to anterior exenteration. Reasons for routine removal of the prostate include direct extension of the bladder cancer into the prostatic urethra, as well as prostatic ductal or stromal involvement. There is also a risk of secondary malignancy, namely, prostatic adenocarcinomas, which has been detected in up to 40% of specimens in historical cases.

A better understanding of the anatomic relationships of the neurovascular bundles with respect to the prostate combined with improved surgical technique has led to major improvements in functional outcomes. Retaining potency in men following radical cystectomy is also technically feasible and involves careful attention to the area of the prostatic pedicles, where nerve bundle injury is most likely. Currently, it has been reported that potency is preserved in about 50% of men with nerve-sparing techniques and there has been no apparent compromise in cancer control.

Urinary reconstruction following cystectomy involves the reconnection of the ureters to an intestinal segment that allows for the drainage of urine. There are essentially three methods in which this can

be accomplished: an ileal conduit, a continent cutaneous reservoir, or an orthotopic urinary diversion. Historically, a majority of patients underwent an ileal conduit, an incontinent form of urinary drainage. Over the past decade, however, continent urinary diversions, especially orthotopic bladder reconstruction, have evolved from experimental surgery to become a commonly performed method of urinary diversion. The detection of cancer in young patients, the desire to maintain a normal body image, and the realization that quality of life can be improved by maintaining near-normal function after radical surgery, and improved surgical techniques have all contributed to the realization that continent urinary diversion is an option for a significant percentage of patients.

Patient selection criteria include both patient factors and cancer factors. An absolute contraindication in a male patient is the inability to achieve a negative cancer margin in the proximal urethra (prostatic apex). Relative contraindications to orthotopic urinary diversion include renal insufficiency, hepatic dysfunction, and the inability to perform self-catheterisation should the need arise. Although controversial, age alone is not a contraindication to orthotopic diversion and thus can be performed judiciously in men over 70 years of age, and even in men with

significant co morbidities. Prior pelvic radiation therapy is again a relative contraindication; however, there have been reports of successful orthotopic diversion in the setting of salvage cystectomy for failed radiation.

Orthotopic neobladder construction involves the creation of an internal reservoir from some segment of bowel, most commonly this is 45 to 60cm of ileum, detubularized and fashioned in either a “ W configuration” (Hautmann) or “ U shaped or J shaped” (Studer). At Cancer Institute, a “ sperm shaped” neobladder is fashioned. While in the past there was a fear that orthotopic diversion would be associated with a significantly higher rate of complication as compared to an ileal conduit, recent reports suggest that in properly selected patients the early complication rates are similarly acceptable.

The functional results following orthotopic urinary reconstruction have been excellent. Daytime urinary continence rates range from 80 to 95% with differences largely due to definition of continence, methods in which data are obtained, and length of follow-up. Nighttime continence is more problematic, with rates of 65 to 85% reported. The incidence of

hyper-continence or urinary retention requiring self-catheterisation is approximately 3 to 5%. Men should be counseled preoperatively that while most men are continent in the day, they may experience some degree of incontinence at night and a protective pad may be required. Overall patient satisfaction with orthotopic neobladder substitution remains high with >95% of patients satisfied with their choice of diversion.

In women, radical cystectomy for muscle invasive bladder cancer has historically been equivalent of an anterior exenteration. This includes removal of the uterus, fallopian tubes, ovaries, bladder, urethra, and a segment of anterior vaginal wall. This remains the gold standard. However, early detection combined with a desire to improve the functional outcomes, including sexual abilities and urinary control, has led surgeons to modify their techniques in selected patients, where preservation of disease-free urethra is possible.

Although the majority of women still undergo ileal conduit urinary diversion or continent cutaneous diversion, orthotopic urinary diversion has become increasingly viable as an option. Exclusion criteria for orthotopic neobladder reconstruction include tumor involving the bladder neck, diffuse Tis, and a positive bladder neck margin at the time

of radical cystectomy. In addition, females with large , palpable tumors along the anterior vaginal wall are not appropriate candidates. In properly selected patients, local recurrence rates have been extremely low and function outcomes have been comparable to those reported among males patients.

The technique and outcomes of orthotopic diversion in females have well been described. These technical refinements include avoidance of overlapping suture lines, the interposition of a vascularised omental pedicle, and preservation of anterior vaginal wall. In patients with non palpable tumors, the plane between the posterior bladder wall and the anterior vaginal wall can be developed while ligating the posterior-lateral pedicles. The plane is developed to the level of the bladder neck, and the anterior and posterior dissections are connected with preservation of the bladder neck.

In most women, the risk of gynaecologic involvement of urothelial malignancy is small and can usually be determined either preoperatively or at the time of surgery. The potential for improved functional outcomes and quality of life through preservation of gynaecological organs, particularly among young women with invasive bladder cancer, is

currently an area of ongoing research, and these younger women are more likely to be concerned about preservation of fertility and continuation of normal hormonal status.

In properly selected patients, functional outcomes have been comparable to those among male patients. Daytime continence rates range from 70 to 95%, with high rates of overall satisfaction. There may be a higher rate of urinary retention regarding intermittent catheterizations, and all patients undergoing diversion should receive preoperative counseling regarding this, as well as other possible complications.

Although it has long been a standard part of radical cystectomy, pelvic lymph node dissection has garnered more attention recently. This is derived in part from data demonstrated long-term disease-free survival among node-positive patients and benefit implied from the completeness of the lymph node dissection. It has been proposed that the therapeutic benefit of lymphadenectomy may be extended beyond the confines of the traditional pelvic template arguing in favour of a more extended node dissection. Recent studies have proposed that the actual number of nodes harvested may play a role in patient outcomes, and the greater the lymph nodes removed the better the survival.

The concept of lymph node density, defined as the total number of positive lymph nodes divided by the total number of lymph nodes removed, has been reported to be an important prognostic indicator among patients with node-positive bladder cancer. The benefit of an extended dissection may be derived from both the removal of clinically apparent pathologic nodes and/or from undetected micrometastatic disease. Future studies that carefully document the overall number and location of lymph nodes removed (mapping) along with the number and location of positive nodes removed at the time of cystectomy using defined templates of dissection and possibly molecular staging will be important.

When performed as a salvage procedure following definitive radiation treatment (>50 Gy), a pelvic lymphadenectomy is not performed because of significant risk of iliac vessel and obturator nerve injury.

For a combined common and pelvic iliac lymphadenectomy, the lymph node dissection is initiated 2cm above the aortic bifurcation (superior limit of dissection), and the dissection extends laterally over the inferior vena cava to the genitofemoral nerve, representing the lateral

limits of dissection. Distally, the lymph node dissection extends to the lymph node of Cloquet medially (on Cooper's ligament) and the circumflex iliac vein laterally.

The long term efficacy of radical cystectomy among patients with invasive bladder cancer has been demonstrated in terms of local control and disease-specific survival. Numerous series have demonstrated excellent local control and excellent 5- and 10-year survivals for patients with invasive bladder cancer treated with cystectomy. Long-term survival is best among those with organ-confined disease, and consistently 5-year survival >70%.

Despite significant decrease in overall mortality and morbidity rates associated with cystectomy, complications can occur as an exacerbation of the patients preexisting co morbid conditions, arising from the bladder removal and those arising from the use of an intestinal segment. The mortality rate for radical cystectomy remains 1% to 2%, with an overall early complication rate of about 25% to 30%.

Radical cystectomy is associated with significant blood loss and/or transfusion requirement, and complicating the surgical treatment of these patients is the significant number that have anaemia. Median

estimated blood loss was 600ml (range 100 to 3000ml). Increased estimated blood loss was related to patient age; longer operating time and paralytic ileus. Overall transfusion was required in 30% of patients with a median requirement of 2 units. These data support the need for continued refinement in surgical techniques designed to decrease blood loss, as well as for strategies designed to lower the need for blood transfusion during radical cystectomy.

Although the published data on neoadjuvant chemotherapy do not meet the standard to declare neoadjuvant chemotherapy the new standard of care in muscularis propria bladder cancer, the data in support of benefit are sufficiently compelling that patients should be informed of the potential benefits versus the risks of neoadjuvant therapy as part of the discussion leading to a decision to proceed with cystectomy. Until the completion of a well-designed and well-executed clinical trial(s), sufficiently powered to settle the question, the place of adjuvant chemotherapy will necessarily remain uncertain.

In certain patients, radical cystectomy may not be the best option, and bladder preservation strategies for the treatment of invasive cancer have evolved for several reasons. Advances in the treatment of other

malignancies such as breast and esophageal cancer, have demonstrated the effectiveness of this strategy. In bladder cancer, the majority of patients with recurrent and metastatic disease die of disease that is distant in location as opposed to local. In addition, despite its accepted standard as the treatment of choice, radical cystectomy does not ultimately result in a cure in a large number of patients and still represents a significant operative procedure with associated complications. Many bladder cancer patients are elderly, and although the number is decreasing with improvements in surgical techniques and perioperative care, there are patients “too ill” to undergo radical cystectomy.

Although this approach has its appeal it remains only an option, and radical cystectomy continues to be the standard treatment of choice. Survival data for bladder sparing approach presented in a certain light can first appear promising, but it is difficult to compare directly how patient survival rates differ between bladder-sparing regimens and initial radical cystectomy. This is true when a significant number of patients do eventually require cystectomy, which is in fact delayed by the bladder sparing approach. This strategy often requires a multitude of visits to different physicians requiring often invasive procedures to attempt to

monitor closely the patient's condition and tumor status. In addition, bladder-sparing protocols are not in themselves inherently risk-free and have associated possible complications. To date, no prospective randomized trial has been performed comparing a multimodality bladder-sparing approach with radical cystectomy.

Partial cystectomy is a bladder-sparing surgical approach. This approach could be advocated in a limited group of patients. Those patients who may be reasonable candidates would include small, single tumors, away from the trigone without related Tis. Although bladder capacity may not be enough to maintain normal voiding patterns, this remaining bladder tissue serves as an area for recurrent disease or previously unrecognized disease. Localized recurrence in the form of new tumors or recurrent tumors occur anywhere between 15% and 75% of the time. This form of therapy should not be accepted as a standard treatment choice.

The combination of transurethral resection, radiation, and chemotherapy for bladder preservation has yielded better results than any of the monotherapies with an improved clinical complete response rate. Substantial improvements in local control have been reported with

combined modality therapy. This generally consists of TURBT for debulking with the goal a visibly complete tumor removal followed by radiation treatment with concurrent radiosensitizing chemotherapy. In the studies reported, the most commonly used radiosensitizing drugs have been cisplatin, 5-flurouracil (5-FU), and paclitaxel, used either singly or in various combinations.

The results of trimodality therapy for muscle-invasive bladder cancer have led to further studies utilizing trimodality treatment with improved radiation techniques and the use of newer chemotherapeutic agents in innovative combinations in attempts to improve on the complete response rate and the long-term control rate in the treatment of muscle-invasive bladder cancer.

The absolute contraindication for bladder preservation protocol treatment is hydronephrosis. The relative contraindications are presence of Tis, incomplete TURBT and patients not fit for cystectomy, if the need for the same arises. One-third of patients entering a potential bladder preservation protocol with trimodality therapy, will require cystectomy.

In bladder preservation protocol, patients undergo TURBT. R0 resection is achieved. Radiation treatment is started 2 to 6weeks after TURBT. 50 to 55Gy radiation is given in conventional fractions to the bladder and the regional lymph nodes, and a boost is given to bladder or tumor bearing bladder area. Concurrent chemotherapy is delivered. Response is evaluated during or soon after treatment. If complete response is achieved, no further treatment is given. If the residue is superficial, reTURBT is done. If gross residue is present, then patient is taken up for salvage cystectomy. Multifocality of primary tumor was associated with higher risk for local recurrence.

The quality of life in patients whose bladders have been preserved has been studied in various centers. 78% have compliant bladders with normal capacity and flow parameters. 85% have no urgency or occasional urgency. 25% have occasional to moderate bowel control symptoms. 50% have normal erectile functions.

Lifelong surveillance with cystoscopy is crucial in patients treated with bladder-sparing therapy. Prompt salvage therapy for superficial or recurrent invasive disease likely has prevented a survival disadvantage. The 10-year overall survival and disease-specific survival in bladder-

sparing protocols are comparable to the results reported with contemporary radical cystectomy. For patients of similar clinical and pathological stage, one-third of patients treated on protocol with the goal of bladder sparing ultimately required a cystectomy. A trimodality approach with bladder preservation based on the initial tumor response is therefore safe and appropriate treatment with the majority of long-term survivors retaining functional bladders.

Urinary diversion is necessary in patients who undergo cystectomy for bladder cancer. Alternative urinary drainage may be either temporary or permanent. Permanent forms of urinary diversions can be accomplished by establishing direct continuity between the urinary tract and the skin or, more commonly, by interposing a segment of bowel between the urinary tract and skin. Nearly all segments of bowel have been described for use in urinary diversion, and despite extensive study, no single method or portion is ideal for all patients and clinical settings. The specific method of urinary diversion should be selected based on the indication for diversion, individual patient preference, anatomy, renal function, and overall health.

Urinary diversions can be broadly categorized into those that are continent and those that are incontinent. Continent forms of urinary diversion are achieved with either a continence mechanism to an abdominal stoma or with an orthotopic bladder substitute relying on intrinsic continence after anastomosis to the native urethra. Noncontinent types of urinary diversion generally act simply as a conduit through which the urine exits the body, thus requiring an external appliance to collect the urine. Although continence after reconstruction permits freedom from an external collection bag, these operations may be technically more difficult and associated with higher complication rates. Continent diversion, however, can benefit the patient with regard to psychologic aspects, with preserved self-image and sexuality. Overall, patient report a high level of satisfaction with both continent and noncontinent forms of urinary diversion.

Seiffert first described an ureteroileocutaneous diversion in 1935. The procedure was subsequently popularized by Bricker and remains the most commonly used method of noncontinent urinary diversion. Patient selection, proper stoma location, and careful technique in creating a well-vascularized stoma are all important to the success of the procedure.

An ileal conduit may be contraindicated in patients with a history of regional enteritis or extensive pelvic irradiation. In these situations, a colon conduit may be preferable. The typical stoma is located in the right lower quadrant. The usual site is located along a line from the anterior superior iliac spine and the umbilicus, at the lateral edge of the rectus abdomens muscle. It is important to bring the stoma through the rectus muscle to help prevent the development of a parastomal hernia. In order to minimize the absorptive surface of the bowel in contact with urine, the ileal segment should be as short as feasible. Reabsorption of urinary constituents does not cause a significant problem in patients with normal renal function but metabolic abnormalities may develop in those with renal insufficiency.

Jejunal conduit urinary diversion should be reserved for patients in whom other, more suitable options are unavailable. These include those with prior pelvic irradiation, inflammatory bowel disease, or loss of the middle and distal ureters. Electrolyte disturbances are more common in those with urinary conduits using the jejunum.

The colonic conduit was popularized by Turner-Warwick in 1960. Urinary conduits constructed from large intestine have several potential advantages when compared to those made using small intestine. First,

non-refluxing ureteral anastomoses are possible using either a short tunnel through the teniae coli or the ileocaecal valve. Second, stomal stenosis is less common due to the larger lumen of the colon. Third, a suitable segment of the colon outside of the field of previous abdominal or pelvic irradiation is usually available. When use of the colon is anticipated, a preoperative contrast imaging study of the large bowel or colonoscopy should be considered.

The ileocecal conduit was first described by Zinman and Libertino in 1975. This method utilizes the ileocaecal valve as an antireflux mechanism for the ureters. Other advantages of this portion of the bowel include the constant and abundant blood supply and location in the right lower quadrant, facilitating stoma formation. The ileocecal segment is rarely affected by generalized bowel disorders, such as diverticulitis.

The transverse colon conduit is well suited for patients who have received extensive pelvic irradiation, making the small bowel suboptimal, or situations where the distal ureters are damaged or absent. In situations of inadequate ureteral length, the transverse colon segment can be directly anastomosed to both renal pelvis. The sigmoid colon

conduit should be avoided in patients with a history of pelvic irradiation. A sigmoid colon conduit is also questionable in those undergoing cystectomy because the vascular supply to the rectum may be compromised if the internal pudendal artery is ligated.

Continent cutaneous (non-orthotopic) techniques can be divided into two major categories: (1) urinary diversion into rectosigmoid and (2) continent urinary pouches requiring clean intermittent catheterization.

The rectal bladder urinary diversions allow excretion of urine by means of evacuation. Ureterosigmoidostomy can be regarded as the original continent diversion with reports of this procedure dating as far back as the 1850s. the complications are secondary malignancy, hyperchloremic acidosis, hypokalemia with nephropathy, and pyelonephritis. This procedure offers a simple form of continent urinary diversion when compared with the newer techniques requiring complex refashioning of bowel segments. Currently this procedure is reserved only for those individuals of advanced age where adverse long-term sequalae are less important.

Numerous operative techniques have been developed for continent catheterizable urinary diversions. To perform clean intermittent catheterization, it is paramount that one has good hand-eye coordination. The choice of where to place the catheterizable stoma is based on the preference of the surgeon. The two most common sites are at the umbilicus and in the lower quadrant of the abdomen, through the rectus bulge and below the “bikini” line.

Perhaps the single most demanding technical aspect during creation of a continent urinary diversion is the construction of the continence mechanism. Four surgical techniques have been incorporated to create a reliable, catheterizable continence mechanism: (1) appendiceal (Mitrofanoff type); (2) pseudoappendiceal tubes fashioned from ileum or right colon; (3) intussusepted nipple valve or flap valve, which avoids the need for intusseseption; (4) the hydraulic valve.

In 1982, Kock et al. reported the first 12 cases on their continent ileocecal reservoir, stimulating world-wide interest in continent urinary diversion procedures. However, the initial enthusiasm with this technique is tempered by a complication rate requiring additional surgery in half of patients, primarily for malfunction of the efferent valve. Since

then, the Kock pouch has undergone several modifications. The T-pouch was devised as a novel continence mechanism by the group at the University of Southern California. It was created entirely from ileum. In 1986, Thuroff et al. presented initial results with a cecoileal reservoir (Mainz I pouch) a sutured ileoileal intusseseption valve served as the continence mechanism in the first series of patients. The introduction of the more reliable appendiceal continence mechanism has greatly increased the acceptance of the Mainz I procedure. The preferred stoma site by the Mainz group is the umbilicus.

Several right colon pouches using the valve technology have been described- Indiana pouch, UCLA pouch, Duke pouch, LeBag pouch, Florida pouch, and the Penn pouch. One of the first continent cutaneous pouches to gain wide acceptance in the urologic community was the Indiana pouch developed in 1985 by Rowland et al. the major contribution was the creation of a reliable continence mechanism. The Penn pouch is an ileocecal pouch, described by Duckett and Snyder in 1986. It was the first continent diversion employing the Mitrofanoff principle, wherein the appendix served as the continence mechanism.

Advantages of using the gastric pouch as a urinary reservoir include diminished electrolyte reabsorption, inherent barrier to absorption of ammonium, absence of hyperchloremic acidosis, and reduced bacterial colonization in the acidic environment. Situations favoring consideration of the gastric urinary diversion include extensive irradiation of the lower bowel, preexisting metabolic acidosis or renal insufficiency, and patients in whom shortening the small bowel could result in malabsorption. The construction of reservoirs entirely from stomach has not seen widespread acceptance. Rather, use of stomach segments has been limited to bladder augmentation or as part of a composite reservoir.

Improvement in cosmetic results and documented increases in quality-of-life outcomes will encourage more surgeons to perform orthotopic bladder substitutions. Appropriate attention is given to preoperative patient selection, specific intraoperative surgical details, and most importantly, meticulous postoperative patient follow up. Advances in surgical techniques together with increased understanding of the pelvic anatomy and natural history of TCC, general physiology, and female continence mechanism have resulted in improved functional

outcomes emulating those in men. The ileal low pressure bladder substitute with an afferent tubular segment is easily constructed and has documented good long-term functional results in both sexes.

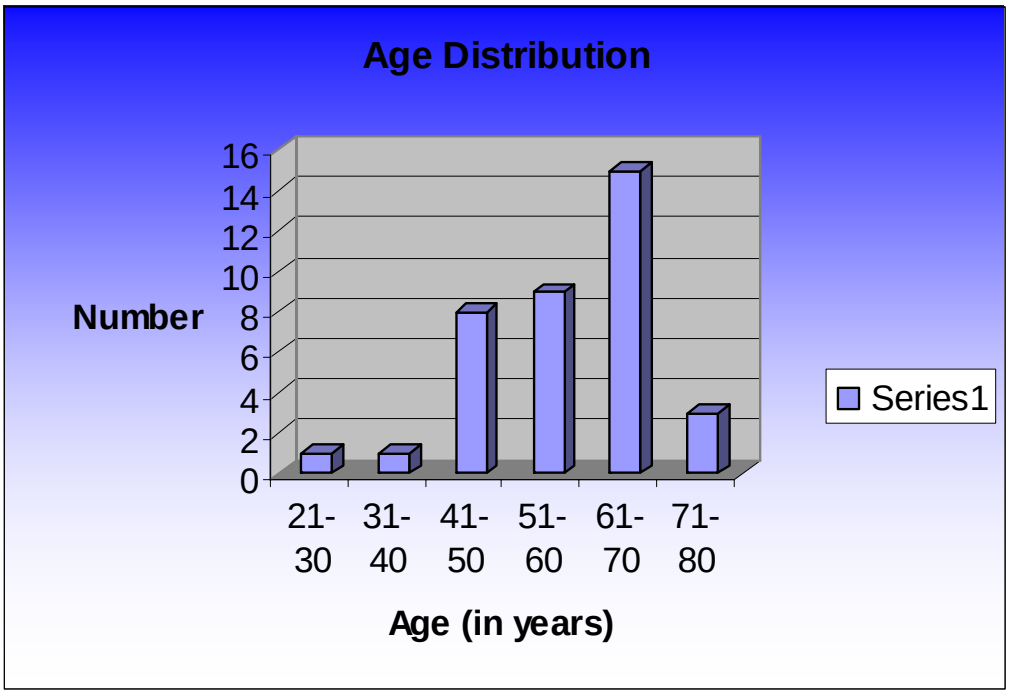
A successful outcome of a bladder substitution requires the cooperation of the patient and the willingness to comply with long-term follow up. The commonest biochemical abnormalities detected following bladder substitution are metabolic acidosis and electrolyte abnormalities. Adequate preoperative renal function is required to limit such complications. Identification of incontinence prior to surgery, especially in females is essential. Urge incontinence is likely to be treated by cystectomy; however, stress incontinence, which is due to inadequate sphincter function, needs to be further evaluated by urodynamic assessment with an urethral pressure profile. Patients with a grade I genuine stress incontinence, a normal functional urethral length, a hypermobile bladder neck and absence of a large cystocele could benefit from a bladder substitute. However, if there is documented evidence for a shortened functional urethral length or intrinsic sphincter deficiency, incontinence following an orthotopic bladder substitute can be expected.

To achieve good functional result, the bladder substitution has to have a good capacity, a low-pressure system made of detubularised bowel segments with minimal outlet resistance and preserved sphincter function. Preservation of the autonomic nerves to the sphincter and urogenital diaphragm is controversial, but it is felt that it should be attempted on the nontumor bearing side (in bladder cancer) as it will increase the chance of potency in the male and aid urinary incontinence in both sexes. Ileal segment is used to create the bladder substitute. A 54- to 56-cm segment of ileum is isolated 25cm proximal to the ileocecal valve. For reservoir construction, a sperm-shaped bladder substitute is fashioned. The in-hospital postoperative period should be utilized for patient education and to help adjust to their bladder substitute. Metabolic acidosis is the commonest biochemical abnormality following a bladder substitution. In virtually all patients, short-term treatment with sodium bicarbonate 2 to 6gm/day will be needed, which is ceased within 3 months time, as the mucosa of the reservoir becomes more resilient to electrolyte and fluid exchange. Diurnal continence of up to 83% in women and 90% in men with nocturnal rates over 80% at 12 months should be achieved in both sexes. Incontinence rates tend to increase in the absence of a nerve-sparing cystectomy, in the older patients and 5

years following a cystectomy. The incontinence is generally minimal and not debilitating with normal transurethral voiding achievable in up to 97% of patients.

Recommended follow up is every 3 months for the first 3 years, then 6 monthly for the next 2 years, and the annually. Clinical examination, urine cultures, body weight and blood gas analysis are recommended at each visit. Chest x-ray and urethral/ureteric wash cytology is done 6 monthly for first 2 years, and then annually. CT scan of the abdomen/pelvis is done annually. Symptomatic cases will require a bone scan for evaluation.

The proportion of patients developing upper tract TCC after the diagnosis and treatment of superficial bladder cancer has classically been reported as 0.002%. Most occurrences present within the first 5 years. Lifelong observation of upper tracts with routine intravenous urograms on a yearly basis or at the detection of positive urinary cytology is required for high risk superficial disease. There are few data to support for such intense follow-up in low-risk patients, but evaluation of the upper tracts on a 3- to 4- year schedule is reasonable.


Age Distribution
Number
16
14
12
10
8
6
4
2
0
21-30
31-40
41-50
51-60
61-70
71-80
Age (in years)
Series1

Recurrence pattern versus grade:

	GRADE 1	**GRADE II**	**GRADE III**
Loco-regional	-	1	5
Distant	-	1	4

Recurrence pattern versus stage:

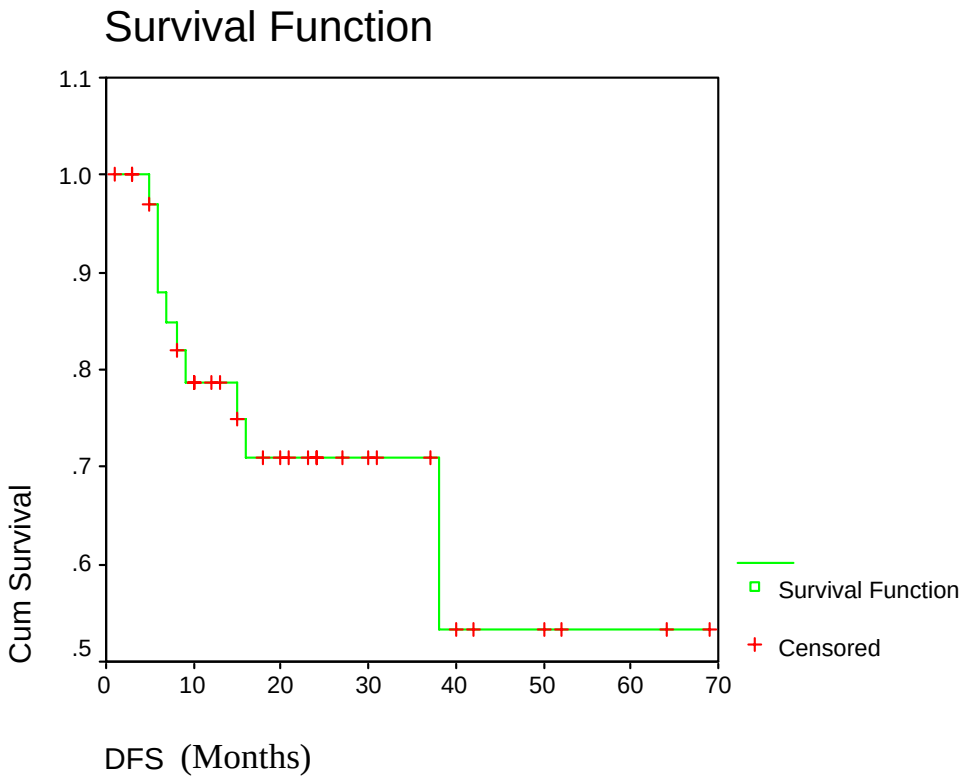
	STAGE I	**II**	**III**	**IV**
Loco-regional	-	1	2	3
Distant	-	3	1	1

Recurrence pattern versus Extent of lymphadenectomy:

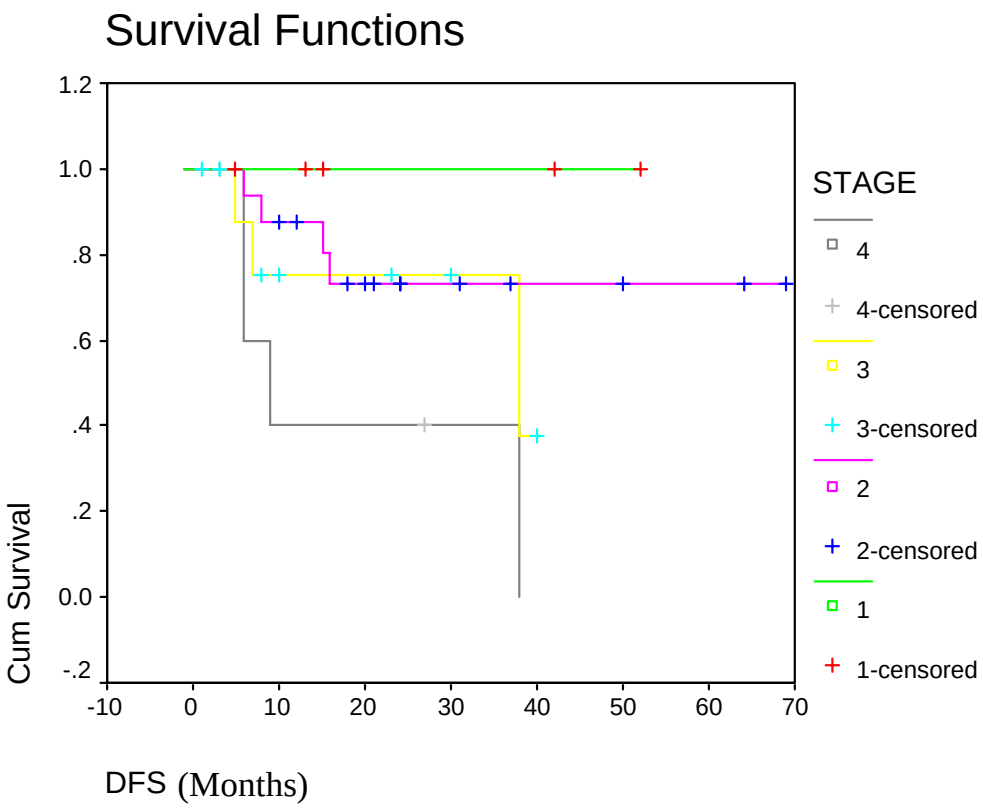
	< 10 LN YIELD	**11-20**	**21-30**	**31-40**
Loco-regional	2	3	1	-
Distant	1	2	1	1

Recurrence pattern versus Pathological nodal status:

	pN0	**pN1**	**pN2**	**pN3**
Loco-regional	2	3	-	1
Distant	4	-	1	-


Survival Function
1.1
1.0
.9
.8
.7
.6
.5
Cum Survival
0
10
20
30
40
50
60
70
DFS (Months)
Survival Function
Censored

SURVIVAL STAGE-WISE



RESULTS

The study includes all patients who underwent radical cystectomy for bladder cancer from January 2001 to March 2007. There were 38 cases in the study. One case was excluded from the study as the final histopathology revealed a leiomyoma of the bladder. Hence there were 37 cases in the study.

The male to female ratio in the study was 5.2:1. The youngest in the study population was 21 year old and the oldest in the study population was 80 year old man. The mean age who underwent surgery was 58 years and the median age was 60 years. The most common presenting complaint was painless haematuria. The mean duration of presenting symptom was 3 months. 13 of 37 patients had co morbid illnesses like diabetes mellitus, hypertension, and bronchial asthma. There was no significant family history of cancer or cancer syndromes.

Of the 37 patients included in the study, 16 of them were smokers. All the smokers were men. The mean duration of smoking was 24 years

Urine cytology was positive in 11 cases. It was associated with grade III disease in 9 cases, grade II in one case and grade I in one case. The sensitivity of urine cytology in this study was 30%. At cystoscopy,20 cases were found to be solitary lesions,&17 of them were multiple. Ultrasound of the pelvis correlated well with the cystoscopy findings. CT scan of the abdomen also correlated well with the cystoscopy findings. Ultrasound and CT scan failed to detect gross pelvic lymph node enlargement in one case, frozen section of the same at surgery was positive for metastatic disease. Chest x-ray did not reveal any abnormality in any of the cases. Bone scan was not done as a routine staging investigation, unless there was any symptomatic bone pain or raised serum alkaline phosphatase that warranted a confirmation. Suspicious uptakes at bone scan were evaluated using MRI scan, and metastatic diseases were eliminated from the study.

37 patients underwent radical cystectomy. Ileal conduit was fashioned in 27 cases. Transverse colon was used to fashion conduit in 2 cases. Orthotopic neobladder was created in 8 patients, which included 5 males and 3 females. The most common indication for radical cystectomy in the study group was muscle invasive-grade III bladder

cancer. Two cases of radical cystectomy was for extensive and inaccessible growths, for whom TURBT was incomplete. The pathologic status of both these cases were pT3. Three cases underwent salvage cystectomy after definitive radiation. One of them had recurrence after radiotherapy and the other two were bladder cripple after radiation. Two of them had transverse colon as conduit. One patient underwent radical cystectomy after due to recurrence after chemoradiation (60 Gy radiation along with 6 cycles cisplatin). The pathological staging after surgery was pT2 and the patient is disease-free at 6 years. Three patients underwent radical cystectomy for recurrence during or immediately after intravesical BCG. A total of six patients had received intravesical BCG before radical cystectomy.

The most common final histology was transitional cell carcinoma (TCC) in 84% cases. Other histological variants in the group were squamous cell carcinoma (SCC), adenocarcinoma and poorly differentiated carcinoma. 70% of the cases belonged to high grade variety. Pathological T status was pT3 in 13 cases, pT2 in 18 cases and pT1 in 6 cases. Pelvic lymph node dissection was done in all cases. Pathological N status was pN1 in 6 cases. They were classified as stage IV as per AJCC classification. One patient had gross pelvic

lymphadenopathy at surgery, frozen section of which revealed metastatic deposits. It was decided to proceed with surgery, and the patient failed in 6 months time with nodal recurrence in the pelvis.

Major postoperative morbidity was seen in 8 cases (21.6%). Most common complication was leak. The incidence of leak was 8%. The other major complications encountered were acute renal failure, vesico-vaginal fistula, deep vein thrombosis, and urinary tract infection. Long term follow up revealed one instance of adhesive intestinal obstruction and incisional hernia repair.

Adjuvant chemotherapy was delivered to one patient whose pathological disease status was pT3N0M0 grade III. 6 cycles of cisplatin and gemcitabine was given. The patient had a disease-free survival of 23 months. Recurrence was locoregional. It is the Institute policy not to deliver neoadjuvant or adjuvant chemotherapy for resectable bladder cancer as of now.

Final pathological stage was stage I 13.5%, stage II 43.2%, stage III 27% and stage IV 16.2%. Surgical staging has upstaged the clinical stage in 43.2%.

All patients were followed up to October 2007 and the pattern of recurrence was studied. 70% of patients did not have any recurrence. 54% had recurrence in the pelvis (locoregional). 45% had failed at distant sites. Pelvic failure was in the form of nodal recurrence. The different sites of distant failure were bone (most common), liver, and CNS. Palliative radiation to pelvic nodal recurrence and spinal metastasis was given in selected cases.

Of the recurrences, 82% had grade III disease at presentation and 18% had grade II disease, signifying grade as a prognostic factor and that high grade disease was associated with poor prognosis and decreased disease-free survival. None of the stage I disease recurred at follow up. 36% of the recurrence belonged to stage II and 27% of the recurrence belonged to stage III.

When the nodal yield was 31-40, there was no instance of loco-regional failure. 16% of loco-regional failure had initial nodal yield between 21-30, 50% had nodal yield between 11-20 and 33% had nodal yield less than 10. This implies that extensive nodal dissection can decrease the loco-regional recurrence. When 1 lymph node has disease, the study revealed failure loco-regional. In the study, one case had 3

positive lymph nodes, and at follow up, the patient had distant failure. One case had gross pelvic lymph nodes at surgery, which were not detected preoperatively. Frozen section of the lymph nodes were positive for metastatic deposits. It was decided to proceed with radical cystectomy, and upon follow up, the patient failed in 6 months due to loco regional failure due to recurrent pelvic lymph nodes.

Of the recurrences, 54% were nonsmokers and 46% were smokers. 72% of the recurrences belonged to the 46-60 year age-group. All the recurrences occurred in the 41-80 year age group.

All patients who had noncontinent diversion in the form of ileal or tranverse colon conduit had high level of satisfaction. There was one instance of parastomal hernia. 8 patients underwent continent urinary diversion in the form of orthotopic neobladder. It included 5 males and 3 females. The oldest patient to have orthotopic neobladder in this series was 65 years. Of these patients, two had incontinence, which included one female. 7 patients had daytime continence of more than 3 hours. Overall, patients with orthotopic neobladder enjoyed a good quality of life.

Cumulative disease-free survival at 70 months in the study was 52%. At 50 months, the disease-free survival for stage I disease and stage II disease was 100% and 72% respectively. At 36 months, the disease-free survival for stage III disease was 74%. Event-free survival at 36 months for stage IV disease was 40% and was zero at 40 months.

DISCUSSION

In India, the crude incidence rate of bladder cancer in males and females is 2.4 and 0.7/100,000 population respectively. In the world, the crude incidence rate of bladder cancer is 25.4 and 8.54/100,000 population respectively. In the Madras metropolitan tumor registry, the crude incidence rate of bladder cancer is 2.1 and 0.8/100,000 population respectively.

The age distribution in the study ranged from 21 years to 80 years. Radical cystectomy can be performed safely, and old age is not a contraindication to this procedure. Co morbid conditions have to be optimized before the surgery.

No relation to family history of cancer or cancer syndromes were noted in the study. The male to female ratio of bladder cancer in this study was 5.2:1. In literature, bladder cancer is more than 2.5 times more common in men than in women.

Urine cytology is reported to have sensitivity of 60% in high grade lesions and 25% in low grade lesions. In this study, urine cytology had an overall sensitivity of 30%. Cystoscopy, USG abdomen and CT scan abdomen were done routinely in all cases as part of the evaluation and metastatic workup. Bone scan was reserved for symptomatic cases of bone pain or in situations of raised biochemical parameters. All patients underwent an initial TURBT with deep muscle biopsy. Muscle invasive bladder cancer were taken up for radical cystectomy. Other indications were incomplete or extensive disease at TURBT, recurrence after radiation/chemoradiation and intravesical BCG. At present there is no policy to deliver neoadjuvant or adjuvant chemotherapy for bladder cancer undergoing radical cystectomy. Noncontinent ileal or transverse colon conduit; or continent orthotopic neobladder reconstruction was fashioned. Overall complication rate in this study was 21.6%. There was no operative mortality. Operative mortality for radical cystectomy has been shown to be between 1% and 3% in most modern series. The overall complication rate after radical cystectomy and urinary diversion in these series may be as high as 25% to 35%.

The most common histology was TCC in 84%. 70% of the bladder cancers in this study comprised of high grade lesions. Stage I comprised

13.5% of cases, stage II 43.2%, stage III 27% and stage IV 16.2%. Surgery has upstaged the clinical stage in 43.2% cases. All patients were followed up to October 2007 and the pattern of recurrence was studied. 70% of patients did not have any recurrence. 54% had recurrence in the pelvis (loco-regional). 45% had failed at distant sites. Pelvic failure was in the form of nodal recurrence. The different sites of distant failure were bone (most common), liver, and the CNS. In reported series, the common sites of distant metastasis were liver (38%), lung (36%), bone (27%) and adrenals (21%). It is estimated that, almost 50% of muscle invasive bladder cancer already have occult distant metastases.

The incidence of loco-regional recurrence in node positive disease after surgery, in this study was 50% and in node negative study, it was 9.6%. In modern series, the loco-regional recurrence in node positive disease after surgery was 20%, and the same in node negative disease was 15%.

Of the recurrences, 82% had grade III disease at presentation and 18% had grade II disease, signifying grade as a prognostic factor and that high grade disease was associated with poor prognosis and decreased disease-free survival. When the nodal yield was 31-40, there was no instance of loco-regional failure. 16% of loco-regional failure had initial

nodal yield between 21-30, 50% had nodal yield between 11-20 and 33% had nodal yield less than 10. This implies that extensive nodal dissection can decrease the loco-regional recurrence. Leissner et al. in his series showed patients with and without local recurrence showed no significant difference in the total number of lymph nodes dissected.

In this study, the disease-free survival for pN1 was 13.3 months and for pN2 was 7 months. Mills et al. in his study did not find any difference in disease-free survival and overall survival between patients who had pN1 and pN2 disease. By contrast, Vieweg et al. in his series of bladder confined primary tumors, there was no difference in survival between pN0 and pN1, but pN2 fared less well. In the presence of pN3 disease at surgery, disease-free survival was 6 months in the study. Similar series report zero disease-free survival at 18 months. With N3 disease detected preoperatively or preoperatively, radical cystectomy was not found to be worthwhile.

Level of satisfaction was found to be high among noncontinent diversion and continent orthotopic bladder substitute in the study. The incidence of incontinence was low and daytime continence was 3 hours. The result was found to be comparable in other studies.

CONCLUSION

The incidence of bladder cancer is low in India and at the Madras Metropolitan Tumor Registry. Radical cystectomy, performed for muscle-invasive bladder cancer has acceptable morbidity, and level of satisfaction with urinary diversion is satisfactory. Pathological stage of the disease and grade of the tumor has a bearing on the recurrence of the disease. Extent of lymph node dissection and pathological nodal status can prognosticate local recurrence. Extended disease free survival is possible in stage I and stage II disease, and after extensive lymph nodal dissection. High loco-regional failure was observed for N3 disease after surgery, which questions the role of surgery in such a scenario.

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PROFORMA

Index No.

Age/Sex:

Presenting complaint-

Duration –

Co morbid illness-

Family History-

Smoking-

Physical Examination-

Urine cytology-

Cystoscopy-

USG Abdomen-

CT Scan Abdomen-

Bone scan-

Chest x-ray-

TURBT-

Intravesical BCG-

Radiation-

Chemoradiation-

Indication for Radical cystectomy-

Date of surgery-

Type of surgery-

Type of urinary diversion and conduit-

Complications-

HPE

Type of histology-

Grade-

Urinary bladder-

Ureter-

Urethra-

Seminal vesicle-

Prostate-

Lymph node status: Pelvic- Para aortic-

Pathological stage-

Adjuvant chemotherapy-

Follow up

Recurrence: Date-

Loco-regional-

Distant-

Management of recurrence-

Date of last follow up-

Condition-

Quality of life-